

THE BATTLE OF THE CELLS.

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IN the year 1846 Dr. Augustus Waller, of London, published a very remarkable paper descriptive of a hitherto unknown power possessed by the white corpuscles of the blood. Watching the flow of the circulation in such transparent tissues as are presented by certain parts of the frog, Dr. Waller beheld what he called the migration of the white corpuscles through the walls of the fine blood-vessels. These migrating cells appeared to pass out from their native channels, and to make their way freely among

the tissues of the animal's body. They behaved themselves as if they were independent organisms, endowed with a vitality separate and distinct from that of the animal of whose blood they formed an essential constituent. This emigrating process—or *diapedesis*, as it was called—naturally attracted much attention. So extraordinary were the phenomena described by Dr. Waller, and so strange, was the idea that the white blood globules could thus wander at their own sweet will through the animal organism,

that it was not wonderful to find the correctness of view of the physiologist-discoverer questioned by some and denied by others.

But the discovery did not remain very long as a doubtful contribution to science. Wharton Jones had described the peculiar movements of these white corpuscles, and Cohnheim, twenty years later, gave an account of the migration process. Many important discoveries in science take their origin from an observation the full meaning of which is not known or appreciated at the time of its first announcement. It was so, I think, in the case of the white blood corpuscles and their errant propensities. The first chapter of the scientific story, written in 1846, has been followed only of late years by a tolerably full development of the plot and incidents of the tale. To-day we are witnessing some of the wonderful and interesting results which have flowed from the researches of Dr. Waller and others half a century ago. It is the general history of these later researches which I propose to narrate in this paper.

A brief study of the microscopic characters of the blood will serve as a suitable preface to our narrative. Under a fairly high power of the microscope, blood is seen to present itself as a fluid clear as water (the *lymph* or *serum* of physiologists), and to derive its color from the presence of an enormous number of microscopic bodies which float in the liquid. These bodies are the red corpuscles. Seen *en masse*, they give to blood its well-known hue. Under the microscope, and spread out in a thin layer, their color is seen to be of a yellowish tint. As regards size, the red corpuscles measure, on an average, about one-three-thousandth of an inch in diameter. Each is a biconcave disk, so that when we look at a corpuscle sideways, it presents something of a dumbbell shape. This description applies to the blood of man and of other mammals at large, except the camel-tribe, which, curiously enough, have red corpuscles not circular in shape, as in other quadrupeds, but oval in contour. Fishes, frogs, reptiles, and birds possess red corpuscles of oval or elliptical shape, and each possesses a nucleus or central particle which is wanting in mammals.

In addition to the red blood corpuscles we find in the blood certain very small col-

orless ones, called "blood platelets." Of these we need take no further notice here; but, existing in the proportion of about two or three to every thousand red ones, we find the white corpuscles of the blood, with the mention of which bodies this article was commenced. These white corpuscles are colorless, and thus stand out in contrast to their red neighbors, which are colored with a substance called *hæmoglobin*, whereof iron is a prominent constituent. But more important is it to note that in its constitution each white corpuscle is a very different body from its red neighbor. It is really a microscopic mass of living protoplasm. It has a nucleus in its interior, and in every respect we may regard it as a living cell. Moreover, it behaves itself as an independent cell, just as the researches of early days informed us. Watched on a specially prepared microscopic slide, we see the white corpuscle flow from one shape to another. In this respect it moves by alterations of its protoplasmic substance, just as does the animalcule we know as the *amœba*, a denizen of stagnant waters everywhere. This likeness of motion to that of the animalcule of the pool has procured for the changes of the white corpuscles the term "amœboid" movements.

Wonderful as it is to think that our blood teems with myriads of these independent living blood cells, it is yet more extraordinary to find that they resemble the animalcule in another respect. The *amœba* eats by engulfing its food-particles with its soft protoplasm body. In like manner will a white blood corpuscle feed itself. It will engulf and ingest solid particles which fall in its way, and will reject indigestible matters. That work which we see the white corpuscle doing on the microscopic slide it effects within the animal tissues. We know now, as Dr. Waller knew in 1846, that, in virtue of its independent life, it can push its way through the soft, delicate walls of capillary blood-vessels and pass into the tissues. In place of regarding these locomotive powers as ways and works of unusual character, we now see that they form part and parcel of the complex living mechanism. While it is the duty of the red corpuscles to carry the oxygen breathed into the blood to all parts of the body, and conversely to convey the waste carbonic-acid gas to the

lungs, there to be exhaled, the function of the white corpuscles is of far more complicated character. They perform a duty which not only lies very close to the maintenance of the organism at large in a natural sense, but which also bears an important relation to its preservation from agencies that perpetually threaten it with disease and death.

In the fresh waters of the world certain small forms of crustaceans are extremely common. The eye may detect these creatures flitting about as mere specks in a tumblerful of water drawn in summer from any brook or pond. These organisms are known, popularly and generally, as "water-fleas," and amongst them one form, the *Daphnia*, or "branch-horned water-flea," is familiar to every microscopist. Its body is clear and transparent, so that the vital processes can be watched in this little creature with little trouble on the part of the observer. Now Metchnikoff, who is chief of the service at the Pasteur Institute of Paris, and a well-known biologist, observed that in the *Daphnia* a curious series of phenomena was occasionally to be noted. In Paris a low form of vegetation allied to the yeast-plant is found in certain waters. It flourishes, for example, in the water of the reptile-tank in the Jardin des Plantes. Here is found, also, the *Daphnia magna*. At certain times, the little crustaceans are noted to present a milk-white color, which, on examination, is found to be due to the presence in their bodies of the spores or youthful forms of the vegetable organism. To this organism the name *monospora* has been given. What is seen in the water-flea is really a case of plant attack on the animal form. The spores bud and grow in the interior of the animal, and, overwhelming it, block up its tissues, and in due season kill it.

When a *Daphnia* has swallowed some of these monospora-spores, they pass into its digestive tube. But when the spores attempt to pass through the tube and to gain admittance to the body cavity of the crustacean, its white blood cells are seen to attack them. One cell may be joined by others, so that the spore in this latter case is actually enclosed and encircled by a multitude of these living corpuscles, which fuse together and form a mass of protoplasm, known as a *giant cell* or *plasmodium*. Within this living environment, single or collective, the spore is

actually destroyed. It is eaten by the white corpuscles of the *Daphnia*'s blood; that animal possessing only white corpuscles, and its vital fluid being of colorless nature in consequence. That this is a real destructive action on the part of the white cells of the crustacean is proved by a very interesting observation. Metchnikoff tells us that if a spore has penetrated through from the digestive system half-way only, so that half of it is still in the intestine and half outside that tube, the half outside which is attacked by the white blood cells is destroyed, while the inside half, not subjected to such destructive influence, remains unaffected. As a rule, the *Daphnia* falls a victim to the attack of the monosporas, notwithstanding the gallant defence against infection which its white blood cells make. But if the animal can gain the slightest advantage in this warfare, the tables are turned on the vegetable invaders. If, for instance, an infected *Daphnia* is removed to pure water and freed from further infection, it often happens that it will completely recover. Its white blood cells free it from the vegetable pests, and restore it to its normal condition.

It is curious to note that other fungi which develop and flourish on the surface of the *Daphnia*'s body are more fatal to its welfare than those which, like the monospora, grow in its interior. Thus there is a fungus allied to that which produces the salmon disease, *saprolegnia* by name, that represents a surface-growth sending rootlike filaments into the *Daphnia*'s body. These roots appear to be much more difficult objects to dispose of than the spores which freely circulate in the blood, where the white cells can meet them on their own terms. Hence the cells are thus placed at a disadvantage. The conditions of battle are unequal between a flourishing external fungus and the cells of the blood; and so the *Daphnia* succumbs much more readily under the *saprolegnia* attack than under the attentions of the monospora and its prolific brood.

From the *Daphnia*, Metchnikoff and other observers, stimulated by the fruits of his work, turned their attention to animals of higher rank in the scale of being. The frog, most useful of animals to the physiologist, was selected for experimentation with disease growths of well-known type. The amphibian is a cold-blooded animal, as everybody knows;

its vital processes are of slower nature than those of warm-blooded organisms, and its structure at large enables the processes equally of health and disease to be conveniently studied. Science, from the days of Galvani onwards, owes a deep debt of gratitude to the humble frog.

The microbes or bacilli selected for experiment on the frog were those of *anthrax*, or "splenic fever." This disease, very fatal to cattle and sheep before Pasteur's system of inoculation came into vogue, is called in man "wool-sorter's disease." Formerly, and before steps were taken to disinfect wool, it was not an uncommon ailment among wool-sorters, and a very serious and most fatal ailment it is in the human being, as in the unprotected quadruped. The rodlike germs or bacilli which are the cause of anthrax are well known to microscopists; their development has been fully studied, and they can be artificially cultivated in various ways. Now, fatal as these bacilli are to many higher animals, on the frog's constitution they have but little effect. In place of dying from splenic fever, or its analogue in amphibian life, the cold-blooded frog simply suffers from an ordinary inflammation, which appears to have nothing specific about it. If the frog is inoculated with anthrax bacilli, the animal, as I have said, exhibits symptoms of local inflammation; but when, after a period, the blood of the animal is examined, white blood corpuscles containing bacilli in their interior are duly discovered.

The analogy between the water-flea combating its vegetable intruders, and the frog fighting the bacilli with its blood cells, was too close to escape notice. Further researches made plain the fact that the warfare seen in the former animal was equally well represented in the latter. Transferred to the microscopic slide, the white blood cells of the frog were seen to surround the bacilli, just as the amoeba of the pool engulfs its food. Examined at a later stage of affairs, the bacilli may be seen to be undergoing degeneration, and to be breaking down in the interior of the white cells. More extraordinary still is the observation that if a bacillus is too long for a white corpuscle easily to engulf it, the microbe will actually be bent round so as to be accommodated to the size of its devourer. Nor is this all. When bacilli which had been partially acted upon by the white cells were

injected into rabbits—animals eminently susceptible to the attack of anthrax—the rabbits remained free from the disease. The clear inference to be drawn from this observation is that the bacilli, which before their capture by the white cells are powerful for evil, are killed by the cells, or at least deprived of the properties to which they owe their disease-producing powers.

I have said that the frog itself is not susceptible to anthrax, and cannot be inoculated with the bacilli of that ailment so as to be made to suffer from the disease. This is the normal state of matters with the amphibian. Possibly as a cold-blooded animal it refuses, in virtue of its own constitution, to succumb to the ailment which is so disastrous to certain warm-blooded forms. In its natural state, therefore, the frog defies the bacilli, presumably because its white cells are able and adequate to protect it from attack. But suppose the conditions of frog life to undergo an alteration which brings it somewhat within the lines of the warm-blooded animal's life, or at least perverts its constitutional powers to a certain extent, then a highly instructive difference is to be noted in its relations to anthrax infection. If the temperature of the frog be heightened by keeping it in a chamber heated to 100° Fahrenheit, and if it be then inoculated with anthrax bacilli, it will die. Thus we see that the white cells have become demoralized by the altered environment of their possessor. They no longer present a bold front to the enemy. Few of them have engulfed bacilli, and the germs run riot through the tissues. The heat, which does not suit the frog, is favorable to the bacilli; and so the weakening of the amphibian's line of defence by the deterioration of its white blood corpuscles leaves it at the mercy of the microbes.

Hitherto I have spoken of the white blood corpuscles under their own and ordinary name. But as science has penetrated deeper into their history a new terminology has sprung up by way of indicating the powers they possess in the way of protecting the animal body against the attack of inimical particles. Thus it is a common practice to speak of all white blood cells as *leucocytes*, while, having regard to their power of devouring foreign bodies, they have been called by Metchnikoff *phagocytes*. The theory of

phagocytosis is therefore noted to be that view of the living organism which maintains the power of its leucocytes, or white blood corpuscles, to eat and devour alien matters that threaten the welfare of the body to which these wondrous living cells belong.

Let us now endeavor to trace the history of these leucocytes backwards, and to note, if possible, the circumstances of their origin and development. Whence do they originally spring in the history of the body's evolution? And how have they come to acquire the habit of defending the organism against the foreign invader? To both of these questions, I think, science can offer a fairly satisfactory reply.

First of all, as regards the individual body of the higher animal, I think we may safely say that the spleen, the lymphatic glands, and allied structures supply the white corpuscles of the blood. These structures are called "blood glands," because they are specially concerned with the renewal of the blood elements. That the spleen manufactures leucocytes, as we may now call the white corpuscles, admits of no doubt. The researches of the Edinburgh School of Medicine particularly, and the names of Hughes Bennett and Sanders, will at once appeal to physiologists in respect of the discovery of the duties of the spleen. We know that the spleen is perpetually turning out white corpuscles, and red ones as well, as part and parcel of its natural function; and we know also that in the disease known as *leucocythæmia* (literally, "white-celled blood"), in which the white corpuscles are vastly increased in number, the spleen is specially affected. This last condition of white-cell increase represents, in one phase at least, the increased and abnormal work of that organ. Besides, microscopic examination of the normal spleen pulp shows us blood corpuscles in all stages of break-down and in all stages of formation. I have always likened the spleen to a railway depot where new rolling stock is not only being perpetually manufactured, but partially used stock is also being repaired and old stock got rid of. If the blood is placed in the position of the railway, we may be able to realize the justice of the metaphor.

It is not alone in the circulating blood, however, that we find our leucocytes;

and this observation is a point of some importance, in view of our future researches into the origin of these wandering cells of ours. Lining the blood-vessels is a delicate membrane which is spoken of in science as *endothelium*. There appears to be little doubt that the essential feature of this membrane is its cells, which possess powers and properties analogous to those we have seen to be the inheritance of the leucocytes themselves. Metchnikoff maintains—and I do not know that his opinions have been scientifically questioned in this respect—that many of these cells of the blood-vessels, fixed as they are, can protrude their living substance, and thus capture and destroy, or at least engulf, foreign particles. Very natural it is, I think, that the blood-vessels themselves should be the seat of an action which has so much in common with the powers possessed by the wandering leucocytes. We might, indeed, compare this defending combination of cells to an army, one portion of which remains to protect home interests, while the other portion has a roving commission as free lances, or as a flying column, to make war or to defend whenever opportunity occurs.

The original source of leucocytes, or, rather, the relation they bear in the great scheme of evolution to life at large, is a topic of interest, because we have been enabled to trace with a clear hand the development of these white blood cells in higher organisms from the cells of lower life. Here, as elsewhere, in higher organisms we can trace the abiding influence of lower forms. Just as in the highest beings we can find traces or vestiges of what Darwin called their "lowly origin" in the shape of rudimentary muscles, bones, eye-stalks, and nerve-twigs, so in the matter of the leucocytes we are able to hark back with scientific satisfaction to the beginnings of phagocytosis and its wonders in certain belongings of the animal groundlings.

Let us start with the amoeba once again. This animalcule, as we have seen, is a microscopic fragment of living protoplasm, which, as an independent organism, moves, eats, digests, and reproduces its kind. One and the same bit of protoplasm discharges all the duties of life; and the amoeba, as has been duly noted, is the prototype of the white blood corpuscle or leucocyte itself.

Apart from the fact that all animals start life in the guise of the amoeba—for the ovum or egg is essentially a similar nucleated mass of living matter—we find that our next step upwards brings us into the kingdom of the sponges. Here a mass of amoeba-like specks of protoplasm, forming a colony, secretes the sponge skeleton—limy, horny, or flinty, as the case may be—and, like a collective or compound amoeba, receives and engulfs particles of food which are conveyed to it in the water streams that are perpetually circulating through the canals and waterways of the miniature submarine Venice.

Not far removed above the sponges is the type of animals which owns the common fresh-water polype or hydra, the zoophytes, the jelly-fishes, the sea-anemones, and the corals as its representatives. The body is now better defined, and if we study what occurs in a hydra, we shall be able to note how the amoeba-like power of engulfing food-particles still remains as a permanent feature of the animal. A hydra is a minute living tube, which is fixed by one extremity to a water-weed, and possesses a mouth and tentacles for the capture of prey at the other and free extremity. There are no organs within this tubular body; but that body is built up of cells, which are arranged in an outer layer, the *ectoderm*, and an inner layer, the *endoderm*. Food swallowed by the hydra is deposited in the simple interior of the tube body; but the cells of the lining (or endoderm) are seen to constitute the chief agents in the process of digestion. They throw out processes from their substance, so as to engulf what has been swallowed, and, in fact, comport themselves exactly like stationary leucocytes in our own blood-vessels. Furthermore, digestion may be said to actually occur within these cells. Like the amoeba itself, each cell digests what it has seized in the way of food, and contributes its share of the work of assimilation to the sum total represented by the labor of all the cells. In the hydra, then, the cells of the endoderm lining of the tubular body are decidedly the seat of food prehension, and of food digestion also.

If now the development of a higher animal be studied, we find that the body is really built up by the elaboration of three layers of cells, which result from the

first beginnings of the building process in the egg. There is an outer layer, called the *epiblast*, which gives origin to the nervous system and outer skin. This corresponds with the ectoderm of our hydra. There is an inner layer, called the *hypoblast*, which chiefly forms the inner lining of the digestive organs. This evidently represents the endoderm of lower life. But there is now a third layer, called the *mesoblast*, only faintly developed in lower forms, but out of which arises the great bulk of the body. It is this mesoblast (or mesoderm) from which heart, blood-vessels, and other organs arise; and it is this layer which originates the white blood corpuscles as well. But as the mesoblast itself is simply a development of the two primitive and original layers themselves (ectoderm and endoderm), a direct continuity is thus traceable between the cells of lower life which (as in hydra) digest food and carry on all the body's work, and the cells in higher life, which, sometimes adherent to the wall of a blood-vessel, arrest alien particles, or, more typically, as the leucocytes of the blood, seize upon, eat, and destroy the invading bacilli which threaten their possessor with destruction.

What I argue for here, is the direct continuity of these diverse cells in respect both of origin and habit. They arise in higher and lower life from practically the same layer, and they have retained a remarkable likeness and similarity of habit as well. In lower life, as a single cell like the amoeba, the microscopic speck of protoplasm forms of and by itself a perfect individual. In the hydra there are simply many such cells, eating and digesting as their normal duty in life. In the higher realms of life we see the same action performed by essentially the same cells. That which they accomplish in us as a corps of sanitary police, they effect in virtue of their direct inheritance from their ancestral cells in the amoeba and its kith and kin. The destruction of bacilli in us is only the continuation of the habit and mode of life which these cells acquired in the far-back past, when their duty was limited to feeding the organism of which they constituted an essential part. To-day, in the aristocracy of nature, they have only modified their original habit somewhat. Their duties are not so much nutritive as defensive. They rep-

resent an active sanitary department or board of health, charged with the function of guarding their possessor against the inroads and attacks of the foes which threaten our physical prosperity through the initiation and development of disease.

If we may thus demonstrate that higher life has received this wondrous power of combating its microscopic enemies as a direct legacy from lower organizations, it is also possible to show that the leucocytes, or "wandering cells," of lower animals have many traits akin to those seen in the white cells of higher organisms. I have alluded to the fact that several leucocytes may come together for the purpose of more effective attack on their enemies in the shape of bacilli, and thus form a "giant cell," or plasmodium. This phase of their life illustrates anew the old maxim, *L'union fait la force*. In some mollusks the same action has been noticed to occur. A transparent animal, *Phyllirhoe* by name, fed with granules of carmine, continues to surround the masses of color grains, which are too large for individual leucocytes to ingest, by forming giant cells. One leucocyte unites with another, till the foreign body is surrounded. In man, as in the *Daphnia*, such united cells are found in connection with certain diseased tissues. In tubercle and in leprosy, giant cells are known to occur, and the explanation of their appearance would seem to be most easily arrived at on the idea that they represent the collective efforts of the leucocytes, exercised in the endeavor to get rid of the offending materials of the disease.

To the ancients the symptoms of inflammation were well known. Classic physicians spoke of the four signs of the process as *calor, tumor, rubor, et dolor*—heat, swelling, redness, and pain. The type of the process has not altered since classic ages, for inflammation to-day, as every one knows, still exhibits all four characteristic signs. A simple inflammation soon ends. The symptoms disappear, and the parts return to their normal condition. But when the process proceeds to a further stage we then find "suppuration" to ensue, and the essence of this latter action is the formation of what we know as "matter," or *pus*. The difference between a simple scratch, which heals at once, or, as surgeons say, "by first intention," and a poisoned puncture which develops into a matter-forming ac-

cident, is so well known that any description of the process would be absolutely superfluous. Now the old theories of inflammation attributed the symptoms more or less directly to changes in the blood and blood-vessels and to the outflow into the tissues of the fluid of the blood. These views were, for the most part, unsatisfactory, because they implied certain causes or conditions which were themselves matters of uncertainty and dispute. No doubt there is a determination of blood to the inflamed part, or, as the ancients put it, *ubi stimulus ibi affluxus*; but the why and wherefore of this condition was unknown. What the "pus" or "matter" was which appeared as the result of inflammation was a matter still more doubtful than the mere cause of the inflammation itself. Long ago, I can well remember the late Professor Hughes Bennett, of Edinburgh University, insisting on the fact that under the microscope the cells of pus could not be distinguished from the white cells of the blood. Bennett made an observation here, the gist of which he himself did not appreciate; for, in a word, pus cells *are* white blood corpuscles. They are the leucocytes which have come to grief in their battle against a process threatening the body's welfare.

Suppose we produce an artificial inflammation in a tissue which can be inspected under the microscope: we may see, with Metchnikoff, how the whole inflammatory process is merely a struggle between the leucocytes on the one hand and whatever has caused the irritation on the other. The blood current is seen to slow down; the fluid part of the blood escapes from the vessels, and the white blood cells or leucocytes migrate in numbers from the blood-vessels into the tissues, in search of the offending bodies or substances. At first an inflammation may show us simply the blood fluid, and little else, escaping to form the swelling of the ailment. Later on it begins to become turbid somewhat, and it is then seen to contain a few leucocytes, while finally it becomes true "pus." It forms an abscess, which may be large and serious in extent or simple and insignificant, as in the case of an inflamed pimple. But the pus we discover to be composed simply of the emigrated leucocytes. They are in one sense our defeated sanitarians. They have succumbed to the inflamma-

tory action, and they may, as dead and useless things, constitute of themselves a danger to the organism they endeavored to conserve. Inflammation is thus to be ranked not so much as an unnatural and diseased process, but as one which has a true physiological significance, in that it begins, at least, in an endeavor on the part of our leucocytes to save us from the consequences of infection.

The case has never been more aptly put than by Mr. J. Bland Sutton, who, remarking on the new reading of what inflammation is and means, says that, "zoologically, it should be likened to a battle. The leucocytes are the defending army, their roads and lines of communications the blood-vessels. Every composite organism maintains a certain proportion of leucocytes as representing its standing army. When the body is invaded by bacilli, bacteria, micrococci, chemical or other irritants, information of the aggression is telegraphed by means of the vaso-motor nerves (those governing the movements of blood-vessels), and leucocytes rush to the attack; re-enforcements and recruits are quickly formed to increase the standing army, sometimes two, three, or four times the normal standard. In the conflict cells die, and often are eaten by their companions; frequently the slaughter is so great that the tissue becomes burdened by the dead bodies of the soldiers in the form of pus, the activity of the cell being testified by the fact that its protoplasm often contains bacilli, etc., in various stages of destruction. These dead cells, like the corpses of soldiers who fall in battle, later become hurtful to the organism they in their lifetime were anxious to protect from harm, for they are fruitful sources of septicæmia and pyæmia (blood-poisoning)—the pestilence and scourge so much dreaded by operative surgeons."

The removal of disease products from the tissues of living animals is, however, not the only duty which these phagocytic cells discharge. There is no doubt that in the healing of wounds they play an all-important part. A scratch with a needle is truly a matter of no great moment; yet it is a "solution of continuity," as the surgeon puts it, and as such it may serve as an entrance into the organism of nefarious particles which are capable of producing serious effects. But the healthy scratch soon heals, and the healing pro-

cess is undoubtedly due in great part to the action of our friendly cells. The layer of what is called "lymph" which forms on the surface of the scratch is composed largely of leucocytes. Now if the healing process proceeds favorably, we shall find the cells to become modified, changed, and organized to form the material out of which the cicatrix or scar of the wound is developed. This scar in a slight wound does not remain. It is further disposed of by the formation of the natural elements of the skin substance; but in a wound of serious nature we see how the scar tissue remains permanently to mark the efforts of the leucocytes in the work of repairing the gap.

There is yet another phase of the action of the leucocytes deserving of notice. In the course of development most animals, in passing from their youthful to their adult stages, get rid of certain belongings of immature existence. The first teeth of the higher mammals and the tail of the tadpole afford familiar illustrations of such disappearing structures. It has been found that the absorption of the roots of our first or "milk" teeth, which drop out painlessly in consequence of their roots vanishing away, is due to the action of leucocytes in eating up the useless dental foundations. The tail of the tadpole disappears when the frog begins to assume its terrestrial habiliments. The gills of early life also vanish away when the lungs of the adult stage are developed. Both gills and tail are really eaten away by the leucocytes of the young frog. One can see inside the cells the fragments of the tail muscles which they have devoured. This function of getting rid of the odds and ends and "unconsidered trifles" of animal life is not the least important of the duties discharged by our microscopic allies. It is hard to say how much in the way of physical elevation we may owe to the efforts of these minute beings in removing the useless and effete details of an economy which aspires to leave behind it the "childish things" of its past.

It is highly interesting to note that by some observers the tonsils, situated in the back of the mouth, organs whose functions have hitherto been unknown, are regarded as practically blood-glands, the chief duty of which is the manufacture of leucocytes. The position of the tonsils, it is pointed out, is eminently cal-

culated to give them every advantage of capturing particles of foreign matter, which otherwise would invade the lungs. It is asserted that the tonsillar surfaces are practically covered with living active leucocytes, manufactured in these glands as they are developed in the spleen; so that a regular sanitary *cordon* is thus constituted by the tonsils at the entrance to the lungs, such as can arrest particles whose presence, if not exactly injurious, would at least be undesirable in the respiratory organs. Even in the lungs the leucocytes are seen to engulf such dust particles as may have been inhaled, and these intruding granules are carried by them to the lymphatic glands of the lungs, where they are deposited, and removed from the chances of working further harm, as it were.

The story of the leucocytes and their labors would be incompletely told if reference were not made to the part played by these living cells in insuring us from disease invasion on a wide scale. I may premise that the facts I have chronicled with reference to the work of leucocytes in devouring bacilli, and in acting otherwise as bodily scavengers and sanitarians, are not in dispute. I have simply described what has been seen by competent observers, and what may be seen by any one trained in the use of the microscope. The history of phagocytosis rests on the surest basis of all—that of accurate observation.

Naturally, however, a question has arisen regarding the relation between this phagocytic action of the white blood cells and the immunity or freedom from certain diseases which is exhibited by some animal forms. Is the power of the leucocytes to devour bacilli sufficient to explain such immunity? Or have we to take into account other conditions than the leucocytes themselves and their ways to make plain the why and wherefore of an animal's insusceptibility to certain ailments? These are the questions over which modern science is now exercising itself. Metchnikoff himself, as the leader of what may be called the "phagocytic school," of course strongly advocates the view that it is to the powers exercised by the leucocytes that immunity from disease is directly due. He says that what is called "immunity" is really often only "recovery in operation from the very onset of a disease"; that is to say, the dis-

ease has been present, but the leucocytes have successfully and at once checked its progress by their prompt method of disposing of the infecting microbes. He would explain infection on the theory that an animal's leucocytes do not possess the power of destroying the bacilli. If afterwards the same animal acquires an immunity against that particular ailment, Metchnikoff holds that the effect of vaccination or inoculation has simply been to give its living cells the power of devouring the microbes—how or why, is another matter altogether. He supports his views by the remark that in ordinary rabbits anthrax infection is followed by a very poor attempt on the part of the leucocytes to dispose of the bacilli, whereas in vaccinated rabbits the leucocytes are extremely active, and protect the animal against attack. But even Metchnikoff himself admits that the leucocytes are very susceptible to external influences, and especially to chemical conditions. They are repelled by certain microbes, probably because these bacilli produce some chemical product which protects the germs against the leucocyte attack; and they are attracted by other microbes, whose chemical secretions do not interfere with the destructive operations of the white blood cells. Again, we are told that these two phases of things are not immutable, and that the leucocytes may become accustomed to an influence which at first repelled them. In the latter case they will of course attack and devour the offending microbes.

The real battle of immunity is to-day being fought around the question how far purely chemical conditions represented by the bacilli of disease and by the blood fluid of an animal itself, apart altogether from leucocytes, may serve to explain our original escape from disease, or our acquired immunity from it. Are the leucocytes the primary agents in procuring this freedom from infection, or are they only secondary agents, which take advantage of chemical conditions, with the production of which they have in reality no concern? To this question, I apprehend, no exact or definite reply can at present be returned. But what evidence is at hand from recent researches on what are called the *toxins* of disease seems to point to some modification of Metchnikoff's views being probable as an ultimate result of the controversy. The toxins are

the specific poisons produced in the body of an animal by the multiplication of bacilli. When, therefore, an animal not susceptible to a particular disease is inoculated with the germs of that ailment, the toxins produced must undergo some modification or other which renders them entirely inoffensive to it. Immunity here is due, therefore, in this view of things, not to phagocytic action, and not to any work of leucocytes, but to a purely chemical condition. It has, besides, been found that the blood fluid of an animal which cannot be infected, say with anthrax, actually contains a substance which can be used in making cultures of disease microbes to inoculate susceptible animals against that ailment. The "antitoxin treatment" of diphtheria with the products obtained from the blood of the horse after inoculation with diphtheria germs—the horse itself being insusceptible to the disease—is a familiar illustration of this fact. So that it does not require a very elaborate examination of the evidence already before us to raise doubts whether immunity is always and invariably a consequence of leucocyte action alone on bacilli. It may be that the leucocytes themselves play a chemical part in the process, in addition to their direct action on microbes. It may be that these living cells produce some substance which, given forth to the blood fluid, renders that liquid the direct means of combating the microbes. But the case as it stands strongly suggests the possession by the blood fluid of animals, apart from leucocytes altogether, of properties which act in protecting them from the attacks of certain ailments.

The case of relapsing fever is one which, by way of conclusion, may be taken as typical of the difficulties of the present position of matters. In this disease the special microbe is a corkscrew-shaped organism called a *spirillum*, which possesses motile powers. When the patient suffers from the acute paroxysm or "relapse," the spirilla occur in plenty in the blood. In the alternating and quiet stage they disappear from that fluid. In inoculated monkeys, which suffer, by-the-way, from one attack only without alternating phases, it was found that during the paroxysm the spirilla were free in the blood, while none could be found in the white corpuscles; but when the fever had abated, the spirilla, apparently leaving the

blood, were found in the leucocytes of the spleen. The suggestion here is that at the onset of the disease and during its acute stages the spirilla present in the blood evade capture by the leucocytes in virtue of their movements, while as the disease fades they are captured by the white cells of the spleen, where they are duly disposed of. Phagocytic action alone, on this view of things, would seem to account for the disappearance of the ailment. But the opposing theory holds that the spirilla in the blood undergo some modification or other—quinine appears to produce some such effect—due to the properties of the blood itself, and that their disposal by the leucocytes in the spleen is really only the finishing-touch to microbes previously weakened and rendered practically harmless by the blood fluid.

Admitting that the nature of the protection, original or acquired, against disease which certain animals possess is far from being settled, this fact, we may maintain, leaves untouched the general conclusions with regard to the wonderful actions of the white blood cells I have chronicled in this paper. That they act both in lower life and in higher existence as a veritable sanitary police corps is an accepted scientific fact, founded, as we have seen, on observation. These curious cells may or may not be dependent on the blood fluid itself for much of their power of attacking our microbial visitors, which, like unwelcome and unbidden guests, invade our territory and bring disaster in their train. Sufficiently wonderful, apart from all debatable matters, is the fact that we do possess an array of microscopic allies ready to do battle on our behalf against intruding microbes. How much of that condition we familiarly call "health" is due to the work of our wandering cells is not difficult to guess. The preservation of our physical well-being may be a matter much more closely dependent on the activity of our leucocytes than is generally supposed. Life, complex and intricate as it is, is made up of very small things in more senses than one; and the story of the white blood cells illustrates once more the truth of the saying of Swift, that "man is a microcosm or little world resembling in miniature every part of the great, and the body natural may be compared to the body-politic."